Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Biological Psychiatry

COVID-19 Infection During Pregnancy and Risk of Neurodevelopmental Disorders in Offspring: Time for Collaborative Research

To the Editor:

The current coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has become the worst pandemic since the 1918 influenza pandemic (1). This novel viral infection, first reported in December 2019 in Wuhan, China, spread around the world in just a few months, causing an overwhelming international health crisis that could affect up to one-third of humanity (1,2). COVID-19, which causes fever and mild to severe respiratory symptoms, is closely related to other coronaviruses (CoVs), such as SARS (SARS-CoV-1) and MERS-CoV (Middle East respiratory syndrome CoV) (1). Cumulative studies have demonstrated that acute respiratory virus infections such as CoVs and influenza can lead to long-term neurological and neuropsychiatric symptoms (3–5). Moreover, there is evidence suggesting an association between prenatal exposure to these respiratory infections and an increased risk of neurodevelopmental disorders in offspring, such as schizophrenia, bipolar disorder, and autism (4,6). The potential for over 100 million women currently pregnant around the world to be exposed to COVID-19 (2) raises concerns about the possible increased risk of neurodevelopmental disorders in their offspring.

A number of different mechanisms have been proposed to explain how maternal infection may interfere with brain development in the offspring: 1) systemic allostatic overload with loss of structural and functional placenta integrity, 2) activation of the maternal and fetal immune responses with the production of neuronal antibodies and proinflammatory cytokines, and 3) interference in the fetal neurodevelopment by direct brain infection (3,6–8). However, there is currently limited evidence regarding the risk of intrauterine vertical transmission of SARS-CoV-2, and whether the virus has neuroinvasive potential via retrograde axonal transport from peripheral nerves or via a hematogenous route is the subject of ongoing debate (1,9). Thus, attention should focus on how COVID-19 infection could affect the fetal brain through the loss of placental integrity or activation of immune/inflammatory response. Special consideration should be given to the role of cytokines and activation of fetal microglia, mast cells, and astrocytes; changes in placental neurotransmitter production; the consequences of prolonged fever, hypoxia, hypertension, electrolyte abnormalities, and changes in the microbiome; and the effects of medication employed to treat the infection (6,8,10). It should further be noted that most of the data currently available concern neonatal and delivery outcomes from low-quality studies of pregnant women infected by COVID-19 in their third trimesters (9). Therefore, the impact of prenatal exposure to SARS-CoV-2 in fetal neurodevelopment is practically unknown, especially in pregnant women infected during the first and second trimesters.

Prevention and control of the COVID-19 pandemic are major worldwide health problems, and interdisciplinary approaches are needed to develop effective epidemiological strategies against the virus. Beyond this, and prioritizing the concern for adverse fetal brain development in pregnant women infected with SARS-CoV-2, assessment of the neuropsychiatric complications in their offspring has become paramount. Thus, the pandemic provides an unprecedented context for clinical and translational research to further explore the mechanisms underlying breakdowns in fetal neurodevelopment during maternal infection, unknown partly because of methodological constraints of previous studies (3,6). Cohorts of COVID-19–infected pregnant women may currently provide biological (e.g., umbilical cord and placenta samples) and clinical (e.g., maternal serum samples and neonatal filter paper blood samples) data that would enable the acquisition of very valuable genetic, metabolic, and immunological information. Such information would help determine the extent to which maternal infection, in addition to genetic vulnerability, contributes to an increased risk of neuropsychiatric disturbance in the offspring, and would improve our understanding of the role of immune-inflammatory mechanisms during pregnancy in the etiology of neurodevelopmental disorders (10). It would thus be possible to overcome the limitations of previous research and find the answers to some relevant unresolved questions: Is there a sensitive period, and is maternal exposure to infection during early pregnancy more harmful than later exposure? Is the male placenta (XY) more sensitive than the female placenta (XX) to the effects of the prenatal infection? Could this be the underlying cause of sex differences in the prevalence of mental disorders? Is the risk of neurodevelopmental problems during maternal infection higher in those offspring with a family history of neuropsychiatric disorders? How does this genetic risk interact with maternal inflammation and other perinatal and postnatal contributors? Does the effect of gestational exposure to infection differ among ethnic and cultural groups? If so, what would be the role of health disparities on offspring neurodevelopmental abnormalities?

Now is the time to design and implement an agenda for future collaborative research on prenatal effects of COVID-19 on neuropsychiatric outcomes (Box 1). Such population-based birth cohort studies of SARS-CoV-2–infected pregnant women should involve detailed systematic clinical and biological examinations during pregnancy and delivery along with an extended follow-up of the offspring, including neurocognitive, neuroimaging, and electrophysiological examination. They could also include different racial, ethnic, and socioeconomic groups, as well as direct comparison with offspring of noninfected pregnant women. These research projects could offer a great opportunity for a better understanding of the role of maternal infection in the etiopathogenesis of brain disorders. Moreover, they could contribute to establishing risk factors, improving diagnostic specificity, and designing innovative treatment methods. Because all these challenging goals can only be tackled with more robust

https://doi.org/10.1016/j.biopsych.2020.09.011
ISSN: 0006-3223

Box 1. Highlights for Future Research

Epidemiological studies have found that prenatal exposure to acute respiratory infection is linked to a range of neurodevelopmental and psychiatric disorders. However, the etiopathogenic mechanisms underlying breakdown in fetal neurodevelopment during maternal infection remains unknown.
Large-scale and long-term prospective population-based birth cohort studies of COVID-19–infected and unaffected pregnant women are needed to unravel the complex interactions between maternal infection and risk of neurodevelopmental disorders in offspring.
Perinatal data collection should include environmental, ethnic, cultural, social, clinical, genetic, and biological information, whereas neurodevelopmental outcomes should be systematically tracked through early adulthood and include neurocognitive, neuroimaging, and electrophysiological assessments.
These research projects could provide valuable information bridging gaps in knowledge of the link between the activation of immune-inflammatory response during maternal infection and the appearance of neurodevelopmental and neurobehavioral symptoms in the offspring. Similarly, they could enable the identification of other early neurodevelopmental biomarkers.
Major challenges to be overcome in these studies will be logistical and financial barriers to their implementation, such as standardization of procedures for data and specimen collection during the perinatal period across sites, participant long-term commitment, and operating costs of long-term routine follow-ups.
To tackle goals and overcome obstacles, these studies should be developed within a collaborative multidisciplinary framework including basic science, preclinical, translational, and clinical research. Moreover, they should preferably be carried out under the auspices of international organizations with access to adequate funding resources.

COVID-19, coronavirus disease 2019.

transdisciplinary collaboration, we suggest that research groups include gynecologists and obstetricians, neonatologists and pediatricians, child and adolescent mental health professionals, and immunologists, microbiologists, and molecular biologists. Likewise, because logistical and financial barriers to such ambitious goals may be numerous, we urge development of these population-based birth cohort studies of COVID-19–infected pregnant women within a framework of large-scale internationally funded projects (Box 1).

Álvaro López-Díaz
Rosa Ayesa-Arriola
Benedicto Crespo-Facorro
Miguel Ruiz-Veguilla

Acknowledgments and Disclosures

The authors report no biomedical financial interests or potential conflicts of interest.

Article Information

From the Unidad de Gestión Clínica Salud Mental (AL-D), Hospital Universitario Virgen Macarena; Instituto de Biomedicina de Sevilla (AL-D, BC-F, MR-V); Unidad de Gestión Clínica Salud Mental (BC-F, MR-V), Hospital Universitario Virgen del Rocío; Departamento de Psiquiatría (BC-F, MR-V), Universidad de Sevilla; and Centro de Investigación Biomédica en Red de Salud Mental-CIBERSAM (AL-D, RA-A, BC-F), Seville; and Instituto de Investigación Marqués de Valdecilla-IDIVAL (RA-A), Santander, Spain.

AL-D and RA-A contributed equally to this work.

Address correspondence to Benedicto Crespo-Facorro, M.D., Ph.D., at benedicto.crespo.sspa@juntadeandalucia.es.

Received Jul 20, 2020; revised and accepted Sep 9, 2020.

References

1. Wu Y, Xu X, Chen Z, Duan J, Hashimoto K, Yang L, *et al.* (2020): Nervous system involvement after infection with COVID-19 and other coronaviruses. Brain Behav Immun 87:18–22.
2. Boelig RC, Manuck T, Oliver EA, Di Mascio D, Saccone G, Bellussi F, Berghella V (2020): Labor and delivery guidance for COVID-19. Am J Obstet Gynecol MFM 2:100110.
3. Khandaker GM, Zimbron J, Lewis G, Jones PB (2013): Prenatal maternal infection, neurodevelopment and adult schizophrenia: A systematic review of population- based studies. Psychol Med 43:239–257.
4. Parker SE, Lijewski VA, Janulewicz PA, Collett BR, Speltz ML, Werler MM (2016): Upper respiratory infection during pregnancy and neurodevelopmental outcomes among offspring. Neurotoxicol Teratol 57:54–59.
5. Troyer EA, Kohn JN, Hong S (2020): Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun 87:34–39.
6. Kępińska AP, Iyegbe CO, Vernon AC, Yolken R, Murray RM, Pollak TA (2020): Schizophrenia and influenza at the centenary of the 1918-1919 Spanish influenza pandemic: Mechanisms of psychosis risk. Front Psychiatry 11:1–19.
7. Brown AS, Meyer U (2018): Maternal immune activation and neuropsychiatric illness: A translational research perspective, 2018/09/18. Am J Psychiatry 175:1073–1083.
8. Khambadkone SG, Cordner ZA, Tamashiro KLK (2020): Maternal stressors and the developmental origins of neuropsychiatric risk. Front Neuroendocrinol 57:100834.
9. Kotlyar A, Grechukhina O, Chen A, Popkhadze S, Grimshaw A, Tal O, *et al.* (2021): Vertical transmission of COVID-19: A systematic review and meta-analysis. Am J Obstet Gynecol 224:35–53.e3.
10. Shallie PD, Naicker T (2019): The placenta as a window to the brain: A review on the role of placental markers in prenatal programming of neurodevelopment. Int J Dev Neurosci 73:41–49.